REMARKS

Claim Status

Claims 1-33 are pending. Claims 3, 13, 14, 26-30, 32 and 33 stand withdrawn.

Claim Objection

Claim 1 stands objected to under 37 C.F.R. § 1.75 as allegedly being a substantial duplicate of claim 2. Applicants respectfully traverse this objection.

Claim 1 differs from claim 2 in that it includes the claim element of "subsequently culturing or maintaining said cells" whereas claim 2 recites "culturing said cells." Therefore, claim 1 is not a substantial duplicate of claim 2.

In view of the foregoing, Applicants respectfully request withdrawal of the objection.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4-12, 15-25, and 31 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tamamori-Adachi, *et al.* (2003) Circ. Res. 92:e12-e19 ("Adachi") taken with Sutterlüty, *et al.* (1999) Nature Cell Biology 1: 207-214 ("Sutterlüty"); Sherr, *et al.* (1999) Genes & Development 13:1501-1512 ("Sherr"); Flink, *et al.* (1998) J. Mol. Cell. Cardiol. 30: 563-578 ("Flink"); and Poolman, *et al.* (1999) Circ. Res. 85: 117-127 ("Poolman"). Applicants respectfully traverse this rejection.

Adachi does not teach or suggest the claimed invention.

The Office Action asserts that the Adachi teaches a method for proliferating cardiomyocytes *in vitro* comprising introducing a cyclin (linked to nuclear localization signal) and a cyclin-dependent kinase (CDK) using two separate adenovirus vectors. Office Action at pages 3-4. The Office Action concedes that Adachi "differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip family proteins into cardiomyocyte cultures." Id. at page 4.

Applicants agree that Adachi does not teach the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into cardiomyocytes. Indeed, Adachi does not teach or suggest the involvement of the Cip/Kip family protein (e.g., $p27^{Kip1}$) in the proliferation process of cardiomyocytes. Rather, as discussed in the specification,

Adachi discloses a method of proliferating cardiomyocytes comprising the expression of a cyclin and a CDK. See, e.g., page 3, line 13 to page 4, line 18.

Sutterlüty does not remedy the deficiencies of Adachi.

Sutterlüty does not teach or relate to methods of proliferating cardiomyocytes. Indeed, Sutterlüty discloses that mammalian fibroblasts forced into quiescence by serum starvation can be driven into S phase by ectopic expression of the F-box protein $p45^{SKP2}$. Id. at page 213. Sutterlüty observes the effect of the loss of $p27^{Kip1}$ on the proliferation of quiescent fibroblasts, but is silent with respect to cardiomyocytes. Sutterlüty at Figure 1. Further, Sutterlüty does not teach or suggest to a person of ordinary skill in the art to use the F-box protein $p45^{SKP2}$ for the purpose of inhibiting p27 expression in cardiomyocytes. Thus, Applicants submit that Sutterlüty does not solve the deficiencies of Adachi.

Sherr does not remedy the deficiencies of Adachi.

Sherr, like Sutterlüty, is silent on cardiomyocytes and does not teach methods of proliferating cardiomyocytes. Sherr discloses that CDK inhibitors of the Cip/Kip family are inhibitors of cylcin E- and A-dependent CDK2 but positive regulators of cyclin-D-dependent kinases. Id. at 1501. Thus, Applicants submit that Sherr does not solve the deficiencies of Adachi.

Flink does not solve the deficiencies of Adachi.

Flink discloses that cardiomyocytes retain the capacity to proliferate until the early neonatal period when a series of changes lead to terminal differentiation including a switch in pRb partners, a decrease in CDK levels, and an induction of CDK inhibitory activity. Id. at page 563. Applicants submit that this references provide general background for the role of p27 in cell division cardiomyocytes. Thus, Applicants submit that Flink does not solve the deficiencies of Adachi.

Poolman does not solve the deficiencies of Adachi.

The Office Action states that Poolman teaches the loss of the $p27^{Kip1}$ gene results in the proliferation of cardiomyocytes. Office Action at page 5. The Office Action asserts that

Poolman therefore provides sufficient motivation for one of ordinary skill to introduce a gene encoding a factor that inhibits the production or function of the $p27^{Kip1}$ to the cardiomyocyte system of Adachi. Id.

Applicants respectfully disagree. As an initial matter, Applicants submit that Poolman does not directly prove the increase in the number of cardiomyocytes is due to the loss of the $p27^{Kip1}$ protein. At best, Poolman discloses that the loss of the $p27^{Kip1}$ gene in neonatal mice results in such an increase. The loss of the $p27^{Kip1}$ gene alone, however, is not sufficient for the efficient proliferation of cardiomyocytes. Indeed, the specification demonstrates that almost no increase in the cell number of cardiomyocytes was observed where the production of $p27^{Kip1}$ gene product was inhibited by infection with p27 siRNA alone. See Example 5 and Figures 9 and 10; see also page 82, lines 8-11. In contrast, the specification teaches that by the co-expression of D1NLS and CDK4, the inhibition of $p27^{Kip1}$ ($p27^{Kip1}$ siRNA infection) caused a significant increase of the cell number of cardiomyocytes. See, e.g., Figure 10; see also page 82, lines 5-7 (" ... the cell number of cardiomyocytes with the three genes namely D1NLS, CDK4 and p27 siRNA genes expressed therein was significantly increased."). Accordingly, Poolman does not teach or suggest that introducing a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein promotes the proliferation of cardiomyocytes.

Applicants also submit that Poolman observes the effect of the loss of $p27^{Kip1}$ on the proliferation of cardiomyocytes only in postnatal mice, but not in adult mice. *See* Poolman at Figures 7-9. Indeed, the cardiomyocytes in adult mice have generally lost their growth activity. On the other hand, the claimed invention is applicable not only to neonatal cardiomyocytes, but also to adult cardiomyocytes. Furthermore, the specification discloses a therapeutic effect on damaged cardiomyocytes, i.e., the heart functions of the damaged animal model are maintained by the method of the invention. See Example 6, Figures 11-13 and Table 1 of the specification. These effects are neither taught nor suggested by Poolman. Applicants further submit that Poolman fails to teach or suggest combining his $p27^{Kip1}$ gene silencing method with any other method, let alone with a method of co-expressing cyclins and/or CDKs. Thus, Applicants submit that Poolman does not solve the deficiencies of Adachi.

The combination of Sutterlüty, Sherr, Flink, and Poolman does not solve Adachi's deficiencies.

Applicants submit that Adachi taken with Sutterlüty, Sherr, Flink, and Poolman, alone or in any combination thereof, do not teach or suggest each and every claim limitation at least because the secondary references do not teach or suggest the claimed therapeutic methods or vectors. Furthermore, Applicants submit that one of ordinary skill in the art would have no reason to combine these references. Even assuming one of skill in the art had a reason to combine the teachings of any combination of these references (and this combination taught each and every limitation), which Applicants do not concede, the reference would not teach each and every limitation.

Applicants note that the Office Action rejected claims 17-21 over Adachi in view Sutterlüty, Sherr, Flink, and Poolman. These claims are directed to vectors comprising a cyclin gene, a CDK gene and a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein. Further, Adachi does not teach a vector comprising a cyclin gene, a cyclin-dependent kinase gene, and one or a plurality of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein. In contrast, Adachi teaches two separate adenovirus vectors, one comprising cyclin D1 and a different one comprising CDK4. See, e.g., Adachi at "Adenoviruses" at page 2. The Office Action, however, does not provide any reason why the combination of Adachi and Sutterlüty, Sherr, Flink, and Poolman teaches or suggests such vectors. Further, none of the four reference, Sutterlüty, Sherr, Flink, and Poolman, teach vectors.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this response, the Examiner encouraged to contact the Applicant's undersigned representative to discuss and resolve such issues.

It is believed that no additional fees are necessary for the submission of this response. However, should the USPTO determine that any additional fees are due in connection with this response, the Commissioner is hereby authorized to charge such fees to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

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